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General discussion –
The revised role of left ventricular dilatation and ACE-inhibition after myocardial infarction in the thrombolytic/primary PCI era

Pieter-Jan de Kam, Adriaan A.Voors,
Dirk J. van Veldhuisen, Martin St. John Sutton
Wiek H. van Gilst

Submitted

ABSTRACT

Many studies have investigated the process of left ventricular (LV) dilatation and the effects of angiotensin converting enzyme (ACE) inhibitors after myocardial infarction. It has been generally accepted that progression of LV dilatation is a major predictor of heart failure and death after myocardial infarction and that one of the main mechanisms by which ACE-inhibitors produce their beneficial effects is by attenuation of LV dilatation. However, these studies were performed before thrombolytic therapy and primary percutaneous coronary intervention (PCI) were routinely used after acute myocardial infarction. Nowadays reperfusion is obtained much more frequently and LV dilatation after myocardial infarction has become less important. Nevertheless, ACE-inhibitors proved to be effective in terms of reducing cardiac morbidity and mortality. Therefore, mechanisms other than attenuation of LV dilatation such as prevention of progression of atherosclerosis or plaque stabilization may be more important to explain the long-term beneficial effects of ACE-inhibitors after myocardial infarction.

In the present overview, we evaluate the role of LV dilatation and the effects ACE-inhibitors after myocardial infarction in the thrombolytic/primary PCI era and provide recommendations on ACE-inhibitor use in clinical practice.

INTRODUCTION

Acute myocardial infarction is often followed by complex alterations in left ventricular (LV) architecture, often referred to as LV remodeling. Especially, after large anterior infarctions, LV remodeling may become a generalized progressive process, continuing over months to years after myocardial infarction, eventually leading to heart failure and death [1,2]. An integral part of LV remodeling is LV dilatation. During the last decades, many randomized controlled trials have been conducted to investigate the effect of various interventions on the progression of LV dilatation, cardiac morbidity and mortality. These trials have led to two major advances into the treatment of myocardial infarction. First, early myocardial reperfusion of the infarct-related artery (e.g. by administration of thrombolytic therapy or direct percutaneous coronary intervention (PCI)) proved to be an effective way to prevent or minimize LV dilatation and reduce cardiac morbidity and mortality after myocardial infarction by limiting the infarct size [3-8]. Second, angiotensin converting enzyme (ACE) inhibitors showed attenuation of LV dilatation and reductions in cardiac morbidity and

mortality, especially in patients with LV dysfunction and/or in patients without routine administration of thrombolytic therapy [9-12]. However, after early reperfusion, the extent of residual LV dilatation is often limited, and additional reduction of LV dilatation by ACE-inhibitor treatment may be negligible [13,14]. Therefore, the beneficial effects of ACE-inhibitors after myocardial infarction must be caused by other mechanisms than attenuation of LV dilatation.

In the present overview, we will evaluate the role of LV dilatation and the effects ACE-inhibitors after myocardial infarction in the thrombolytic/primary PCI era. Based on the evidence obtained from post-myocardial studies performed during the last few decades and new insights of studies performed in the thrombolytic era, we will provide recommendations on ACE-inhibitor use after myocardial infarction.

DISCUSSION

The process of LV dilatation

The complex changes in morphology of the heart after myocardial infarction is called LV remodeling and aims to restore left ventricular stroke volume and to reduce wall stress to compensate for the loss of systolic function [15,16]. LV remodeling can be divided in infarct zone expansion, non-infarct zone dilatation and LV hypertrophy. LV dilatation is the resulting increase of LV volume over time due to these alterations in left ventricular morphology. The process of LV remodeling starts immediately after the onset of acute myocardial infarction with infarct zone expansion, the main determinant of LV dilatation in the first few days after myocardial infarction [17,18]. Within seconds of a coronary artery occlusion, wall motion abnormalities occur and an overall increase in LV dimensions can be observed [19]. This early form of LV dilatation compensates for the locally damaged myocardium and usually results in a normalized stroke volume [20]. During the following days scar formation occurs as response to the inflammatory reaction and edema in the infarct related area by proliferation of fibroblasts, an increase in collagen fibers and resorption of necrotic tissue [21]. After a few days, continuing wall stress may cause LV remodeling to become a more global process, which may also progress after healing of the infarct region, by non-infarcted zone dilatation [15,22]. Therefore, after the first days following myocardial infarction, non-infarcted zone dilatation is the main determinant of LV dilatation. Dilatation of the non-infarcted area appears to be primarily dependent on the size of the the infarcted area [23] and preceding infarct expansion [24]. In addition to dilatation of the

infarcted and non-infarcted areas, left ventricular hypertrophy is an integral part of the remodeling process. Left ventricular hypertrophy can be considered a compansatory mechanism for the loss of functional myocardium by increase in wall thickness and reducing wall tenderness in order to prevent further progressive dilatation.

Often LV dilatation is a self-limiting process which predominantly occurs in the first month after myocardial infarction, and is evident after infarctions of at least moderate size (affecting 20-40% of the left ventricle) in the antero-apical region [25]. In patients with small infarctions (affecting <20% of the left ventricle), early LV dilatation may regress and long term changes in LV size may be minimal or non-existent [26]. Conversely, chronic LV dilatation may occur after large infarctions (affecting >40% of the left ventricle) and may result in alteration of the contractile properties of the non-infarcted zone and the loss of systolic and diastolic performance of the left ventricle, eventually leading to heart failure and death [1,2].

Effect of early reperfusion on LV dilatation

The most effective way to reduce LV dilatation is to limit infarct size by early reperfusion of the infarct related artery by thrombolytic therapy or primary PCI. Administration of thrombolytic therapy within the first hours after myocardial infarction proved to be effective in limiting infarct size with improvements in regional and/or global ventricular function [4,27-31]. In addition, primary PCI showed comparable reductions in infarct size and even more pronounced improvements of ventricular function than thrombolytic therapy, probably due to the higher patency rate and the less severe residual stenosis [32].

Both early and late reperfusion of the infarct-related coronary artery have been shown to reduce the extent of LV dilatation [3-8,33-37]. The results of almost 14000, mainly thrombolysed patients included in the echocardiographic substudy of GISSI-3 showed relatively no change in LV size after a median of 10 days after myocardial infarction (Fig. 1). Interestingly, even patients predicted to be at high risk of long-term LV dilatation showed only limited progression of LV dilatation after 10 days. These results indicate that, in the thrombolytic/primary PCI era, LV dilatation is a short-term process, limited to the first few days after infarction. Moreover, in the thrombolytic/primary PCI era, long-term LV dilatation may be restricted to a very selected group of high risk patients. Similarly, we showed minimal 3-months changes in LV size after successful thrombolysis in 845 mainly first anterior myocardial infarction patients (Fig. 2) [13].

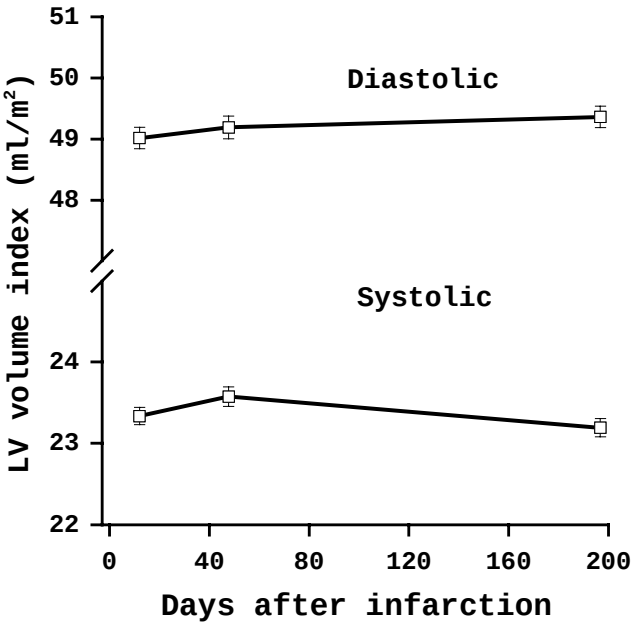

Figure 1: LV dilatation after myocardial infarction in the GISSI-3 echocardiographic populatioN

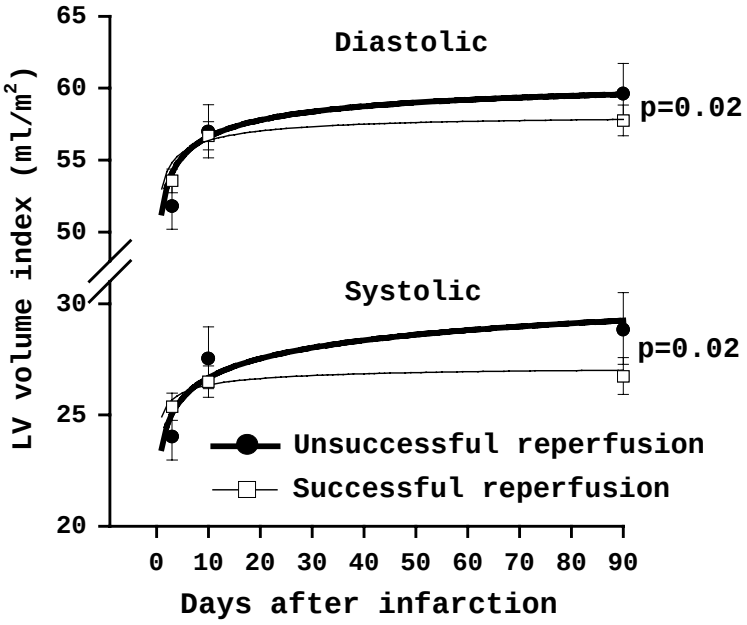

Figure 2: Difference in progression of LV dilatation after myocardial infarction in patients with – and without successful reperfusion

It has even been suggested that extensive LV dilatation despite early administration of thrombolytic therapy is indicative for unsuccessful thrombolysis [38]. Hence, these findings suggest that in the current thrombolytic therapy/primary PCI era, most patients will achieve successful thrombolysis, resulting in smaller infarct sizes and consequently non-existent or minimal short-term LV dilatation after myocardial infarction (Fig. 3).

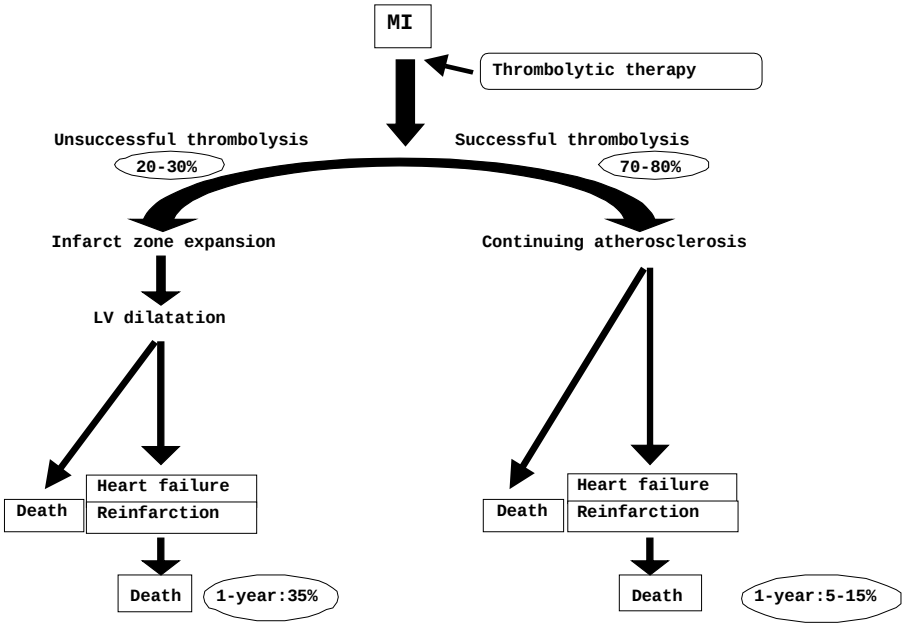

Figure 3: A schematic overview of the generally accepted major pathways after myocardial infarction, extended to the thrombolytic era

Although LV dilatation remains an important predictor of mortality after administration of thrombolytic therapy [14], in the echocardiographic sub-population of GISSI-3 we found that heart rate at baseline was a more powerful predictor of 6-months mortality than the extent of LV dilatation [39]. This important result may indicate that the extent of LV dilatation after myocardial infarction has become a less important predictor of mortality, due to the decreased prevelance of subjects with extensive LV dilatation after the routine administration of thrombolytic therapy.

Effects of ACE-inhibitor on LV dilatation

Several studies have assessed the effect of ACE-inhibitors on LV dilatation using different treatment strategies and patient populations [11,14,25,40-55] (Table 1).

Table 1. Results of placebo-controlled studies assessing the effect of ACE-inhibitors on selected and unselected patients on LV dilatation after myocardial infarction.

Author	Patients	Thromb. therapy/PCI	Sample size	drug	Follow-up	Onset ACE-inh.	Result
Sharpe (40)	EF<45%	0%	90	Captopril	12 months	9 days	Positive
Sharpe (25)	EF<45%	0%	40	Captopril	12 months	>3 days	Positive
Pfeffer (41)	Ant MI/ EF<45%	17%	59	Captopril	12 months	>3 days	Negative
Sogaard (42)	EF<45%	80%	64	Captopril	6 months	>3 days	Positive ESVI Negative EDVI
Sogaard (43)	EF<45%	81%	58	Captopril	6 months	>3 days	Positive Q-wave MI Negative non-Q-wave MI
Calcera-Thomas (44)	PWP≤17 mmHg Ant MI	100%	40	Captopril	2 weeks	<24 hours	Positive
Oldroyd (45)	All MI	0%	99	Captopril	2 months	<24 hours	Negative
Ray (46)	All MI	0%	99	Captopril	12 months	<24 hours	Positive
Ambrosioni (11)	All MI	0%	204	Zofenopril	12 months	<24 hours	Positive EF<40% Negative EF>40%
Bonarjee (47)	All MI	61%	201	Enalapril	6 months	<24 hrs	Positive EDVI Negative ESVI
Sharpe (48)	All MI	72%	100	Captopril	3 months	<48 hours	Positive
Nicolosi (14)	All MI	75%	6405	lisinopril	6 months	<24 hours	Positive EDVI Negative ESVI
Kyriakidis (49)	All MI	86%	78	Captopril	1 month	>3 days	Negative
Schulman (50)	All MI	88%	32	Enalapril	1 month	<24 hours	Positive ant. MI Negative inf. MI
Kleber (51)	All MI	95%	208	Captopril	3 months	<3 days	Positive EDVI, Negative ESVI
Van Gilst (52)	Ant MI	100%	298	Captopril	12 months	< 6 hours	Negative
Borghi (53)	Ant MI	100%	285	Fosinopril	3 months	<9 hours	Negative
Darasz (54)	Ant MI	100%	47	Captopril	6 months	>3 days	Negative
French (55)	All MI	100%	493	Captopril	3 weeks	<6 hours	Negative

MI=myocardial infarction;EF=ejection fraction;ant=anterior;inf=inferior;PWP=Pulmonary wedge pressure

Many of these trials selected patients on decreased LV ejection fraction and most of these trials were performed without routine administration of thrombolytic therapy/primary PCI. Beneficial effects of ACE-inhibition on LV dilatation were demonstrated in selected subgroups of patients with decreased ejection fractions not receiving thrombolysis after myocardial infarction. However, none of the trials in unselected patients or in patients selected on anterior myocardial infarction could demonstrate attenuation of LV dilatation by ACE-inhibitors after routine administration of thrombolytic therapy [52-55]. In addition, our recently performed meta-analysis in 845 patients of three comparable echocardiographic studies with routine administration of thrombolytic therapy showed no difference between ACE-inhibitor and placebo on LV dilatation (Fig. 4) [13].

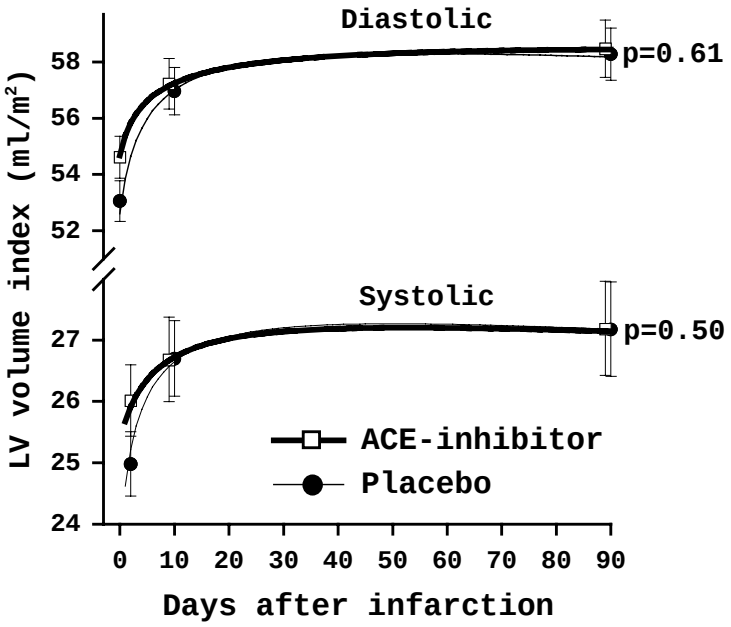

Figure 4: The effect of ACE-inhibitor on LV dilatation after systematic administration of thrombolytic therapy

Effects of ACE-inhibitors on cardiac morbidity and mortality

The mortality results of the large ACE-inhibitor trials after myocardial infarction are summarised in Figure 5. The first group of four studies included symptomatic and asymptomatic high risk patients allocated to long-term treatment with ACE-inhibitors or placebo [9-12]. These studies showed that after myocardial infarction about a yearly mortality reduction of about 5% can be achieved by administration of ACE-inhibitors in patients selected on LV function or anterior infarct location. The second group of four studies included unselected patients allocated to short-term treatment with ACE-inhibitors or placebo/open label treatment [56-59]. These studies showed that less than 1% of the lives could be saved per year by administration of ACE-inhibitors. Only the two largest studies could demonstrate a statistically significant short-term survival benefit [56,58]. However, the observed survival benefit in GISSI-3 after 6 weeks of treatment was no longer significant at 6 months after treatment withdrawal.

Treatment with ACE-inhibitors also proved to be effective in reducing the incidence of heart failure, especially in patients selected on LV dysfunction and anterior infarction (Fig. 6).

However, ACE-inhibitors failed to reduce the short-term incidence of heart failure in unselected patients after myocardial infarction. Furthermore, ACE-inhibitors showed their potential to reduce the long-term incidence of re-infarction rates in the SAVE trial (Fig. 7) [9].

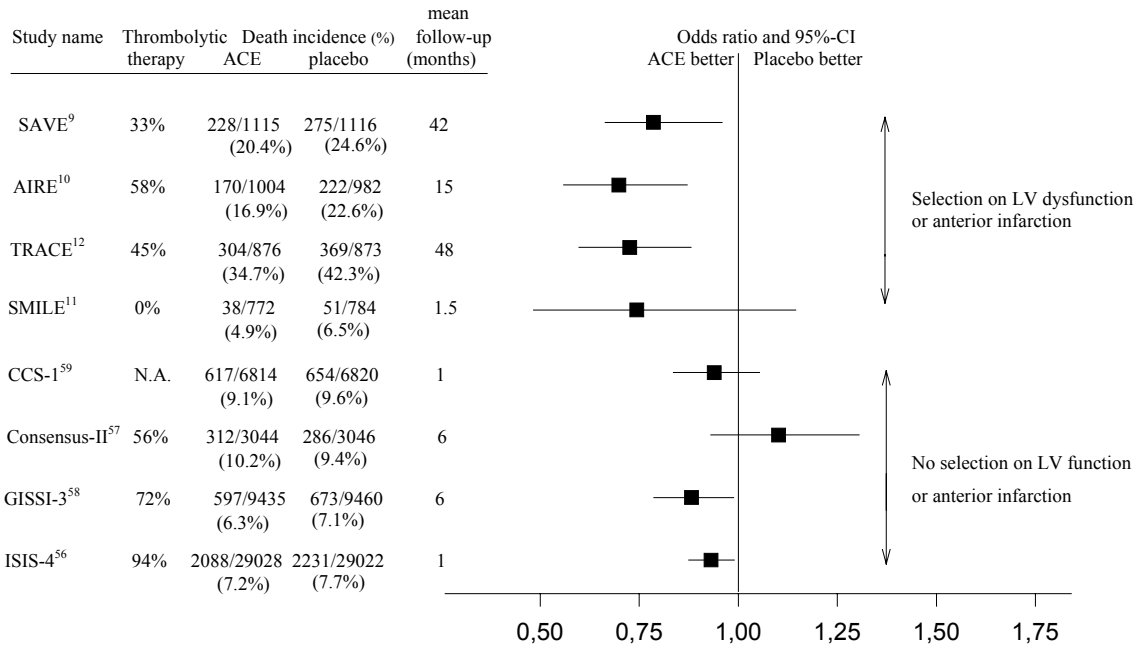

Figure 5: Overview of the mortality results of the large ACE-inhibitor trials after myocardial infarction

Explanations for the effects of ACE-inhibitors

The convincing results of the reduction of cardiac morbidity and mortality in over 10000 patients after myocardial infarction in studies performed in the thrombolytic/primary PCI era cannot be explained by attenuation of LV dilatation, because the prevalence of patients with extensive LV dilatation is low. The exact mechanisms which are responsible for the beneficial effects of ACE-inhibitors on cardiac morbidity and mortality have not been completely resolved yet. Several mechanisms by which ACE-inhibitors may produce their beneficial effects have been described. These effects can be classified into cardioprotective effects and vasculoprotective effects [60]. Attenuation of LV dilatation is a cardioprotective effect and in combination with the reduction of the preload and afterload, ACE-inhibitors realize a reduction in wall stress and reduction of the oxygen demand. In turn, the oxygen supply increases due to vasodilatation caused by reduction of angiotensin II levels.

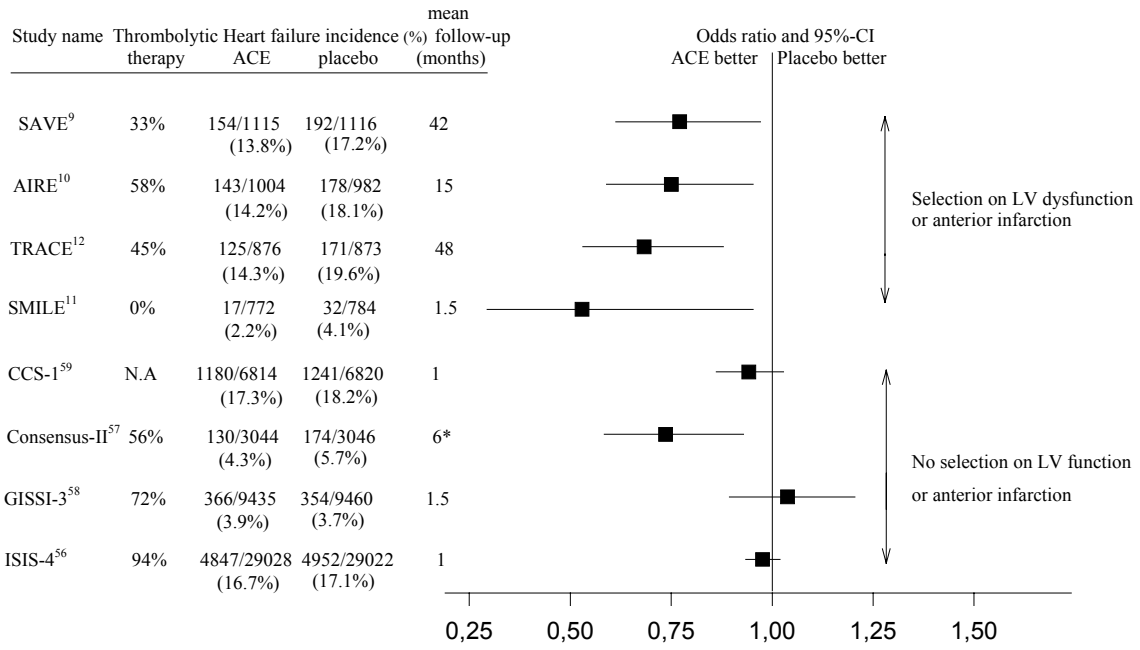

Figure 6: Overview of the heart failure results of the large ACE-inhibitor trials after myocardial infarction; *Only including hospitalisations for heart failure.

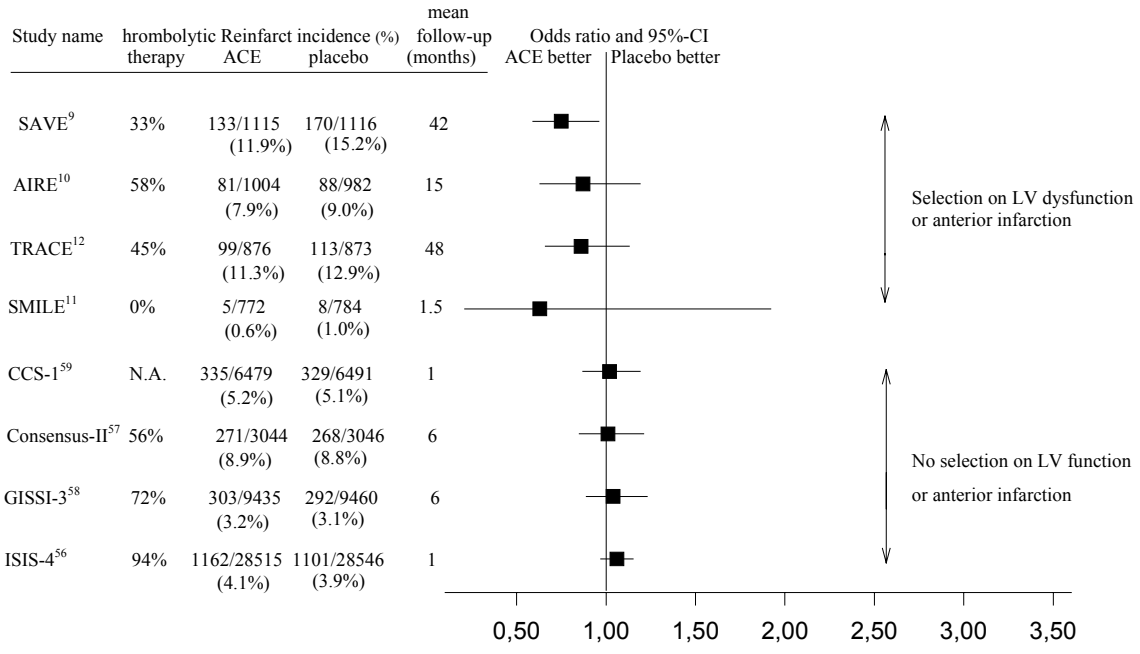

Figure 7: Overview of the results on reinfarction of the large ACE-inhibitor trials after myocardial infarction

In addition to the restoration of the balance between oxygen supply and demand, ACE-inhibitors have consistently demonstrated reductions of ventricular mass in hypertensive patients possibly related to the inhibition of both angiotensin II and aldosterone [61-63]. Furthermore neurohormonal effects have been described of ACE-inhibitors by inhibition of angiotensin II reducing the sympathetic activity [64]. Also reduction of infarct size can be classified as cardioprotective effect of ACE-inhibitors, as well as reduction of reperfusion injury [65]. Other cardioprotective actions are reduction in reperfusion arrhythmias and other ventricular arrhythmias [66,67].

The vasculoprotective effects of ACE-inhibitors all contribute to the prevention of progression of atherosclerosis. Vasculoprotective effects include antiproliferative and antimitogenic action, beneficial effects on endothelial function, plaque-stabilizing effects, antitrombotic effects, effects on the sympathetic nervous system and possible antioxidant properties [60,68]. Several experimental studies indicate that these vasculoprotective effects of ACE-inhibitors may be explained by reduction of the angiotensin II levels and reduction of the breakdown of bradykinin [69]. The reduction of both angiotensin II and the breakdown of bradykinin induces vascular dilatation [69,70], inhibits attraction, adhesion and activation of leucocytes [71,72], inhibits growth of the vascular smooth muscle cells [73,74] and promotes thrombolysis which reduces the formation of thrombus [59,75].

We speculate that in the thrombolytic/PCI era, the vasculoprotective effects of ACE-inhibitors are more important than the cardioprotective effects to explain their long-term effects on cardiac morbidity and mortality. This is largely supported by the results of the HOPE trial, enrolling patients with high vascular risk [76]. After 4.5 years of ramipril use, this study showed 25% risk reduction for cardiovascular death, 20% for myocardial infarction and 32% for stroke. Therefore, in patients with vascular disease, including myocardial infarction, long-term treatment with ACE-inhibitors is associated with reduced progression of vascular dysfunction and consequently improved prognosis.

ACE-inhibitors for whom?

The large ACE-inhibitor intervention trials showed large mortality benefit for high risk patients after myocardial infarction. Translating these results into clinical practice, ACE-inhibitor should be prescribed for all high risk patients who are hemodynamically stable and without clear contraindications to their use, after routine administration of thrombolytic therapy/primary PCI and/or other recommended therapies.

Primary prevention with ACE-inhibitors is indicated for the following groups of high risk patients: 1) patients with signs of heart failure/depressed ejection fractions, 2) patients for whom thrombolytic therapy/primary PCI failed to achieve reperfusion, and 3) patients presenting with large (anterior) infarctions. Furthermore, as secondary prevention for coronary artery desease, ACE-inhibitors can also be prescribed to all other myocardial infarction patients who are hemodynamic stable and have no contraindication to their use [76].

Early or late administration of ACE-inhibitors?

Optimal timing of ACE-inhibitors after myocardial infarction remains a very controversial issue. In three of the four large mortality trials in selected patients, ACE-inhibition was started relatively late (≥3 days after myocardial infarction) [9,10,12]. These trials showed important long-term beneficial effects on cardiac morbidity and mortality. In contrast, in unselected patients with early administration of the ACE-inhibitor (<36 hours after myocardial infarction) showed relatively small short-term beneficial effects on cardiac morbidity and mortality. The first large clinical trial, in unselected patients with ACE-inhibitor administration within 24 hours after the onset of myocardial infarction, was terminated early due to the absence of a survival benefit after 6 months [57].

Although the results of this second group of studies with early administration of ACE-inhibitor showed that most of the survival benefit is already evident after the first day of treatment [77], no large mortality trials have investigated the effect of ACE-inhibitors administrated within a narrower window than within 24 hours after myocardial infarction. However, we showed that treatment with ACE-inhibitors within 9 hours after myocardial infarction in mainly thrombolysed patients resulted in two-fold increased re-infarction rates [78]. This adverse effect of acute ACE-inhibitor treatment was especially evident in the subgroup of patients with small infarct sizes. Hence, the generally accepted strategy is to start ACE-inhibitor treatment within 24-36 hours after myocardial infarction [79]. However, our results suggest that a safer strategy would be to start ACE-inhibitor treatment between 9 and 36 hours after myocardial infarction only in high risk patients. For secondary prevention of coronary artery disease, ACE-inhibitors may be initiated later than 36 hours after myocardial infarction for lower risk patients.

Long-term or short-term treatment with ACE-inhibitors?

Although previous studies suggest to continue long-term ACE-inhibitor treatment only for high risk patients [80,81], we would recommend to continue long-term ACE-inhibitor treatment for all patients after myocardial infarction.

This recommendation is based on the results of the large ACE-inhibitor trials cardiac morbidity and mortality trials combined with the convincing results of the HOPE trial. The mortality studies in selected high risk patients after myocardial infarction showed beneficial effects of long-term treatment with ACE-inhibitors. Interestingly, the SAVE trial could not demonstrate a mortality benefit of captopril treatment after one year. However, after a mean follow-up of 3.5 years, the reduction in mortality risk was shown to be 21% [9]. Also, none of the large trials in unselected patients could demonstrate a reduction of heart failure after 4 to 6 weeks ACE-inhibitor treatment, except for the Consensus II study, the only trial where unselected patients received ACE-inhibitor treatment for 6 months. Furthermore, the unexpected reduction in re-infarction rates by ACE-inhibitor treatment in the SAVE trial became apparent after about 6 months with gradually increasing protective effects of ACE-inhibitors on re-infarction during the 3.5 years follow-up period. The strongest evidence for long-term beneficial effects of ACE-inhibitors was obtained from the HOPE trial, which showed large beneficial effects of 4.5 years treatment with ramipril in patients with evidence of coronary artery disease, including myocardial infarction [76].

CONCLUSIONS

With the routine administration of thrombolytic therapy and increased use of primary PCI after myocardial infarction, the majority of patients achieve successful reperfusion, resulting in small infarct sizes and either non-existent LV dilatation or LV dilatation which is restricted to the first days after myocardial infarction. Therefore, the major role attributed to LV dilatation after myocardial infarction in the pre-thrombolytic era should be revised with systematic administration of thrombolytic therapy or primary PCI. Furthermore, LV dilatation could not be attenuated by ACE-inhibitor treatment in studies performed in thrombolysed unselected patients and in thrombolysed patients with anterior myocardial infarction. However, also in the thrombolytic/primary PCI era ACE-inhibitors remained successful in reducing the incidence of cardiac morbidity and mortality. Hence, these studies support the hypothesis that other mechanisms than attenuation of LV dilatation are responsible for the beneficial effects of ACE-inhibitors on cardiac morbidity and mortality after myocardial infarction. Largely supported by the results of the HOPE trial, one of the main mechanisms by which ACE-inhibitors produce their beneficial effects may be their long-term vasculoprotective action, preventing the progression of atherosclerosis.

Based on these results, we recommend long-term ACE-inhibitor treatment for all high risk patients (with signs of heart failure, ventricular dysfunction, large (anterior) infarction and/or unsuccessful reperfusion) initiated within 9-36 hours after myocardial infarction. Furthermore, we recommend long-term ACE-inhibitor treatment for all other, lower risk patients, initiated later than 36 hours after myocardial infarction. Before starting of ACE-inhibitors, patients should be hemodynamically stable and treated with thrombolytic therapy/primary PCI (if not contraindicated) and/or receive other recommended therapies.

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